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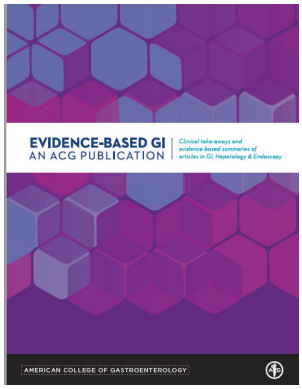

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Underwater EMR for Medium Sized Colorectal Sessile Polyps

Mohammad Bilal, MD, FACG

Associate Professor of Medicine, University of Colorado Anschutz Medical Center, Aurora, CO

Mohammad Bilal, MD, FACG
Associate Editor

COLON

This summary reviews Deng Q, Wu Z, Li J, et al. Underwater endoscopic mucosal resection is superior to conventional endoscopic mucosal resection for medium-sized colorectal sessile polyps: A randomized controlled trial. *Sci Rep* 2024; 14: 30172.

Correspondence to Mohammad Bilal, MD, FACG. Associate Editor. Email: EBGI@gi.org

Keywords: EMR, polyps, sessile polyps, underwater EMR

STRUCTURED ABSTRACT

Question: Is underwater endoscopic mucosal resection (u-EMR) superior to conventional EMR for treatment of medium-sized colorectal polyps?

Design: Open-label, randomized controlled trial.

Setting: Single academic medical center in China.

Patients: Two hundred and sixty-one consecutive patients were assessed for eligibility and 200 inpatients with medium-sized colorectal sessile polyps (between 10 mm to 20 mm) between December 2022 and February 2024 were included. All procedures were performed by 3 experienced endoscopists. Inclusion criteria included those aged 18-70 years who had a sessile polyp between 10-20 mm in diameter. Prior to inclusion pathologic biopsy and digital chromoendoscopy was performed. Exclusion criteria included those patients who

would not cooperate with the protocol, or who had malignant polyps, were on aspirin or with severe cardiopulmonary disease or bleeding diathesis.

Intervention: Patients were randomized to u-EMR versus conventional EMR. U-EMR was performed using saline immersion followed by snare resection using electrocautery. For conventional EMR, submucosal injection was performed using normal saline followed by snare resection using electrocautery. En-bloc resection was attempted first and if not possible, then the lesion was resected in piecemeal fashion. Residual lesion was treated with APC. Decision to perform defect closure was at the discretion of the endoscopist.

Outcome: The primary outcome was R0 resection rate. Secondary outcomes included en-bloc resection rate, R1 and Rx resection rates, visual analogue scale (VAS) of abdominal pain and adverse events. R0 resection was defined as a complete resection of a lesion with lateral and deep negative margins. R1 resection was defined as residual dysplasia under the microscope but no macroscopic residual polyp during colonoscopy.

Data analysis: Quantitative data were compared using the independent sample *t* test or nonparametric Mann-Whitney U test as appropriate. Qualitative data were compared using the chi-square test or Fisher's exact test as appropriate.

Funding: Grants from Maoming City Science and Technology Plan Project (No. 2022138), Baoan District Medical and Health Scientific Research Project of Shenzhen City (No. 2023JD240).

Results: Two hundred patients with medium-sized colorectal sessile polyps were randomly divided into u-EMR group and conventional-EMR group. The R0 resection rate (73.3% vs 56.3%, P=0.011) and the en-bloc resection rate (91.1% vs 80.6%, P=0.032) of the u-EMR group were significantly higher than those of the conventional EMR group. The mean abdominal pain score of the u-EMR group was significantly lower than that of the conventional EMR group [(3.2±1.9) vs (4.1±2.1), P=0.006]; There was no significant difference in the intra-procedure bleeding rate between the groups (4.0% vs 6.1%, P=0.516). There was no delayed bleeding and perforation in both groups.

COMMENTARY

Why Is This Important?

As resection techniques evolve and new ones develop, data regarding their efficacy for colon polyp resection are important for practicing endoscopists. In addition, it is critical to ascertain which techniques are more effective for medium sized colorectal polyps, defined as polyps between 10-20 mm in size. [1, 2] The current study adds to the literature by comparing conventional EMR with u-EMR for removal of these medium sized sessile colorectal polyps. [3] Lastly, this study demonstrated that abdominal pain, an important outcome, is significantly less with u-EMR as compared to c-EMR in this patient group who had minimal or no sedation.

Key Study Findings

U-EMR is superior to conventional EMR in terms of R0 resection rate and en-bloc resection rates for medium sized sessile colorectal polyps.

Patients undergoing u-EMR had less abdominal pain as compared to those who underwent conventional EMR. There was no significant difference in intra-procedural bleeding rate between the two groups.

Caution

The results of the study need to be interpreted with the following caveats. Firstly, the technique of conventional EMR involved submucosal injection of only saline. In the United States saline is mixed with either methylene blue or a commercially available submucosal injectate. It is possible that submucosal injection with a more viscous solution will lead to better resection outcomes (R0 resection and en-bloc resection) with conventional EMR. Secondly, there are no long-term follow up data on recurrence rates, which is an important outcome in resection studies and perhaps the more clinically meaningful outcome. It is however challenging at times to obtain long-term follow up data, and some prior studies have also used biopsy of the base and margin during the index procedure to evaluate for residual dysplasia/polyp. Also, this was a single center study so the results may not be generalizable. Lastly, approximately 20% of the lesions included in the study were sessile serrated lesions (SSLs), and there is ample information that SSLs can be effectively removed with cold snare either using cold snare polypectomy or cold snare EMR. [4, 5]

My Practice

My practice for managing medium sized polyps between 10-20 mm is individualized to the lesion.[6] This includes evaluating the polyp morphology and histology. The Paris classification is typically used to evaluate the polyp morphology. The Paris classification characterizes lesions in the gastrointestinal tract into

three main categories based on their morphologic features: polypoid (type 0 -I), flat (0-II), and excavated (0-III). Type 0-I lesions are lesions that are elevated or protruding and can be further divided as pedunculated (0-Ip) or sessile (0-Is). Type 0-II lesions have flat or superficial surface morphology and can be characterized as slightly elevated (0-IIa), completely flat (0-IIb), or slightly depressed (0-IIc). The last lesion type is excavated (0-III) and indicates ulcerated or excavated lesions.

For polyp histology, the Narrow Band Imaging Colorectal Endoscopic (NICE) classification is used. The NICE classification system uses narrow band imaging to characterize polyps into three types based on their surface features: lesion color relative to background, appearance of blood vessels, and surface patterns. Type 1 lesions usually represent sessile serrated lesions or hyperplastic polyps and are similar in color to surrounding mucosa, have a lacy vessel pattern or lack vessels, and a surface pattern with dark or white spots that are uniform in size. Type 2 lesions are brown relative to background with brown vessels surrounding white structures with an oval, tubular, or branched pattern and are typical of conventional adenomas. Type 3 lesions are brown or black relative to surrounding mucosa with areas of missing or disrupted vessels, have an amorphous or absent surface pattern, and suggest deep submucosal invasion. For polyps with optical diagnosis suggestive of SSL histology, I prefer cold snare polypectomy or cold snare EMR. [1]

I typically use submucosal injection only if the borders of the polyp are subtle and difficult to discern. In those cases, performing submucosal injection allows for better delineation of the polyp. For polyps between 10-20 mm, where optical diagnosis is suggestive of adenomatous histology, I also prefer cold snare polypectomy or cold snare EMR, unless there are features suggestive of advanced histology such as high grade dysplasia or submucosal invasive cancer (non-granular laterally spreading tumors with ulceration, depression or nodular component, NICE type 3 lesions, Kudo pit pattern $V_{N,}$ JNET2b or Paris classification 0 -IIc), in which case I prefer en-bloc resection with conventional EMR.

For Future Research

Future research is needed to compare different EMR modalities for various types of polyps based on size and histology.

Conflict of Interest

Dr. Bilal is a consultant for Boston Scientific, Steris Endoscopy, Aspero Medical and Cook Medical.

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Optimal Colorectal Cancer Prevention With Stool Tests Depends on High Quality Colonoscopy

Dr Joseph Anderson
Co-Editor-in-Chief

Joseph C. Anderson, MD, FACG

VA Medical Center, White River Junction, VT; Geisel School of Medicine at Dartmouth, Hanover, NH; University of Connecticut School of Medicine, Farmington, CT

COLON

This summary reviews Butterly LF et al. Association of endoscopist colonoscopy quality measures with follow-up colonoscopy outcomes after positive stool tests (multitarget stool DNA or fecal immunochemical test): retrospective cross-sectional analysis of data from the New Hampshire colonoscopy registry. Am J Gastroenterol 2024; 119(1): 2215-2223.

Correspondence to Joseph C. Anderson, MD, FACG, Co-Editor-in-Chief. Email: EBGI@gi.org

Keywords: water exchange, colonoscopy, serrated polyp, miss rate

STRUCTURED ABSTRACT

Question: The goal was to examine the association between endoscopist detection rates and polyp yield in colonoscopies performed for positive fecal immunochemical test (FIT) and multitarget stool DNA (mt-sDNA) tests.

Design: This is a retrospective analysis of data from the New Hampshire Colonoscopy Registry (NHCR), a statewide colonoscopy registry.

Setting: Endoscopy centers across New Hampshire.

Patients: The analysis included all patients with a positive stool test as part of usual clinical care from February 2015 to June 2023 and a record in the NHCR of a complete colonoscopy with adequate bowel preparation.

Exposure: The sample included 864 patients with positive mt-sDNA tests and 497 patients with FIT+ stool tests.

Outcomes: The primary outcomes were findings on colonoscopy performed after the stool test, including adenomas, advanced adenomas, and sessile serrated polyps (SSPs).

Data Analysis: Proportions of adenomas, SSPs, and advanced adenomas were calculated for each quartile of adenoma and serrated polyp detection rates by dividing the total number of exams performed by endoscopists within each ADR and SDR quartile with at least one polyp by the total number of exams in that quartile. Proportions were compared across quartiles using the Cochran-Armitage test for trend.

Funding: Exact Sciences provided the funding with an agreement which ensured that the NHCR authors had independence in designing the study, conducting the analyses, and writing and publishing the results.

Results: Polyp detection was higher in exams performed by endoscopists, with higher detection rates for patients who had either positive FIT or mt-sDNA tests. The detection of any adenoma after a positive stool test for endoscopists in the fourth ADR quartile was 63.3% (FIT+) and 62.8% (mt-sDNA+). Among endoscopists in the fourth SDR quartile, SSPs were found in 29.2% of exams following a positive mt-sDNA and in 13.5% following FIT+ exams.

Tips for optimizing polyp detection
Split or same day preparation dosing
Establish quality measurements for detection of adenomas and SSPs
Training in lesion recognition and examination technique
Outstanding basic technique: probing proximal aspects of folds. clean-up, achieve distention
Adequate inspection time
Double examination, particularly the right colon and proximal rectum
Water exchange
Patient rotation
Second observer

COMMENTARY

Why Is This Important?

Stool based tests are recommended by the US Multi Society for colorectal cancer screening.[1] In particular, the two commonly used tests are fecal immunochemical testing with an antibody to human hemoglobin and multi-target stool DNA testing, which has several markers.[2,3] Stool-based tests can be used to increase the prevalence of colorectal neoplasia detected by colonoscopy, thereby selecting that patient who would benefit most from the exam.[4-6] Given the increased role of these tests for screening, data regarding expected polyp yield at colonoscopy are important. While there are many published studies regarding adenoma and SSP detection in FIT-positive patients, similar data for patients with positive mt-sDNA tests are lacking.[7] The data included in this analysis are sourced from the New Hampshire Colonoscopy Registry, a statewide database[8] Consequently, the results provide a real-world perspective on the yield of colonoscopies conducted for positive stool tests. These findings, which show a strong correlation between detection rates and polyp yield, highlight the importance of conducting high-quality colonoscopy.

Key Study Findings

The main finding is that the detection of adenomas and serrated polyps was higher in colonoscopies performed by endoscopists with higher detection rates.

In the top quartile, the detection of any adenoma in colonoscopies performed for mt-sDNA positive tests and FIT positive tests exceed the adenoma detection rate benchmarks suggested by the recent American College of Gastroenterology/ American Society of Gastrointestinal Endoscopy (ACG/ASGE) recommendations of 50% for both tests.[9] These data suggest that 60% adenoma detection rates may be aspirational targets for colonoscopies performed on patients with positive stool tests. The detection of sessile serrated polyps was also high, especially for mt-sDNA positive tests in which more than one in four patients had an SSP. Based on these data, aspirational targets for SSP could be 30% for mt-sDNA positive patients and 15% for FIT positive patients. The lower rates for the other endoscopists, especially in the first and second quartiles, suggest that significant numbers of polyps may be missed by some physicians. Thus, for lower detecting endoscopists, some of these exams with missed polyps may result in the tests being misinterpreted as false positives.[10]

Caution

The low racial diversity in New Hampshire may decrease the generalizability of the findings. Thus, more data are needed in other more racially diverse populations.

My Practice

When performing a colonoscopy on

patients with a positive stool test, I am for looking at lesions that may have triggered the positive test, such as large adenomas or serrated polyps. However, I am also looking for smaller polyps as well. As with all colonoscopies, I carefully interrogate and wash every fold, adequately distend the lumen, utilize an adequate withdrawal time and reintubate the proximal colon as highlighted in the recent ACG/ASGE recommendations.[9,11] In addition, in our endoscopy unit we track our ADR and SDRs and quality of bowel preparation and completion rates, ensuring that we meet established benchmarks.[9,11,12] Thus, when I complete a colonoscopy in a patient with a positive stool test that has no neoplastic findings, I have high confidence that I have not missed important lesions.

For Future Research

A major issue which needs to be addressed is the performance of the next generation of mt-sDNA tests.[13]

Conflict of Interest

Dr Anderson has no financial conflict of interest but he collaborates with Exact Sciences on scientific papers.

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Can Dupilumab Transform Health-Related Quality of Life and Symptoms for Patients With Eosinophilic Esophagitis?

Christopher Vélez, MD
Associate Editor

Noor Syed, MD
Associate Editor

Christopher Vélez, MD[1] and Noor Syed, MD[2]

[1]Associate Program Director, Advanced Fellowship in Functional and Gastrointestinal Motility Disorders, Center for Neurointestinal Health, Division of Gastroenterology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

[2]Gastroenterology Fellow, Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI

This summary reviews Spergel JM, Chehade M, Dellon ES, et al. Dupilumab improves health-related quality of life and a range of symptoms in patients with eosinophilic esophagitis. Am J Gastroenterol 2024;119(12):2398-2407.

Correspondence to Christopher Velez, MD. Associate Editor. Email: EBGI@gi.org

Keywords: Eosinophilic esophagitis, dupilumab, dietary elimination, health related quality of life

ESOPHAGEAL DISORDERS

STRUCTURED ABSTRACT

Question: Among adults and adolescents with eosinophilic esophagitis (EoE), is dupilumab superior to placebo for improving health-related quality of life, reducing dysphagia, and decreasing the frequency and severity of EoE symptoms?

Design: Double-blind, placebo-controlled, randomized controlled trial which lasted for 24 weeks.

Setting: Ninety-six centers across Australia, Canada, Europe, and the United States.

Patients: The LIBERTY EoE TREET study tested use dupilumab in patients >12 years old with a confirmed EoE diagnosis based on >15 eosinophils per high power field (hpf) after 8 weeks of high-dose PPI therapy and a Dysphagia Symptom Questionnaire (DSQ) biweekly total score of ≥10. Patients were stratified by age (adolescent [>12 years and < 18 years old] vs adults [>18 years old]) and current use of proton pump inhibitors (PPIs). Study patients taking PPIs or on an elimination diet could continue these interventions but could not start either upon study entry.

Interventions: Patients were randomized into two parts; Part A: 1:1 ratio to receive either placebo or dupilumab 300 mg weekly and Part B: 1:1:1 ratio to receive placebo, dupilumab 300 mg weekly, or dupilumab 300 mg every 2 weeks.

Outcomes: The primary outcome was the EoE Symptom Questionnaire (EoE-SQ), which assessed the frequency and severity of non-dysphagia symptoms like abdominal pain, bloating, and vomiting, in addition to dysphagia. Secondary outcomes included: (1) the EoE Impact Questionnaire (EoE-IQ), which focused on emotional and sleep disturbances; (2) the Patient Global Impression of Change (PGIC), which gauged patients' perceptions of changes in dysphagia symptoms; and (3) the Patient Global Impression of Severity (PGIS) of Dysphagia, which assessed dysphagia severity during study visits.

Data Analysis: Analyses were performed on an intention-to-treat (ITT) basis using ANCOVA to compare baseline measurements, stratifying by age (≥12 to <18 years and ≥18 years) and PPI use (yes/no) at randomization. Patients requiring rescue treatment had their values censored to avoid bias in the results.

Funding: Sanofi and Regeneron Pharmaceuticals, Inc, the makers of dupilumab.

Results: Dupilumab significantly reduced the frequency and severity of non-dysphagia symptoms (e.g., chest pain, stomach pain, heartburn, regurgitation, vomiting) as measured by the EoE-SQ, with improvements seen as early as week 12 and more pronounced by week 24. The absolute change from baseline to week 24 in EoE-SQ severity exceeded the minimal clinically important difference (MCID) of 5.3 points (LS mean change [SE]: −5.8 [0.71], −5.4 [0.59] for parts A and B, respectively).

Dupilumab also significantly improved HRQoL as measured by the EoE-IQ at week 24, with meaningful reductions in emotional and sleep disturbances. Patients on dupilumab reported less worry about swallowing and choking, and less sleep disruption compared to placebo.

A higher proportion of dupilumab-treated patients reported improvement in dysphagia (PGIC) at week 24, with notably more patients feeling "Very much better" (41% vs 8%, $P < 0.001$, and 44% vs 18%, $P < 0.001$, in parts A and B). Additionally, dupilumab reduced dysphagia severity (PGIS), with more patients reporting no symptoms at week 24 compared to placebo (48% vs 21%, $P < 0.05$, and 36% vs 15%, $P < 0.01$, in parts A and B).

Common adverse events (e.g., injection-site reactions, conjunctivitis, headaches) were mild to moderate and did not lead to significant treatment discontinuations (2.8% in the dupilumab group vs 2.0% in placebo). The safety profile was similar to placebo, with adverse events consistent with previous dupilumab trials.

COMMENTARY

Why Is This Important?

Dupilumab is a monoclonal antibody that has long been used to treat various allergic diseases, including atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis.[2] Recently, it received approval from the U.S. Food and Drug Administration (FDA) for the treatment of EoE.[3] While previous studies have demonstrated the safety and efficacy of dupilumab,[4] this study is the first to examine its direct impact on improving HRQoL, specifically emotional and social aspects, in patients with EoE. There is a strong correlation between symptom improvement and HRQoL measures, highlighting how changes in subjective symptoms are closely tied to patients' overall health perceptions. This finding positions dupilumab as a potentially transformative treatment for EoE, offering benefits that extend beyond just symptom management. The study further underscores the importance of considering both symptom reduction and HRQoL when managing chronic conditions like EoE.

Key Study Findings

Overall, dupilumab not only improved dysphagia but also had a significant impact on reducing other symptoms of EoE and improving the psychosocial and emotional aspects of patients' lives, including sleep and emotional wellbeing (HRQoL) for individuals with EoE.

Dupilumab significantly reduced the frequency and severity of non-dysphagia symptoms (e.g., chest pain, stomach pain, heartburn, regurgitation,

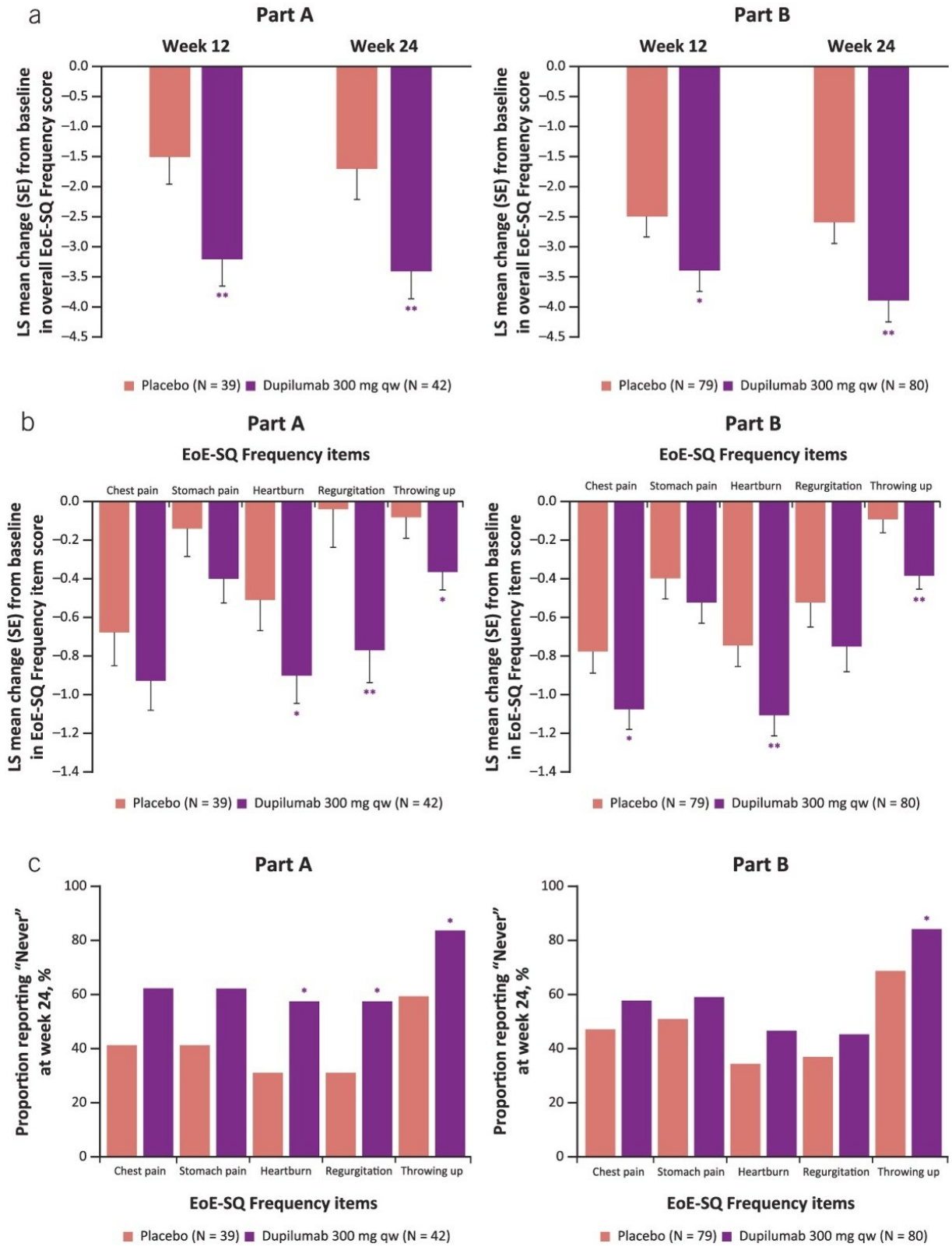

Figure 1. Change from baseline in overall EoE-SQ Frequency score at weeks 12 and 24 (a), individual frequency items of the EoE-SQ at week 24 (b), and proportion of patients reporting never having symptoms assessed by the EoE-SQ at week 24 (c). Note: For proportion of patients reporting never having symptoms, values after first rescue treatment used were set to missing (censoring). Patients with missing score at week 24 are considered as being in the worst possible category (i.e., not included in the "Never" category). *Nominal $P \leq 0.05$, **nominal $P \leq 0.01$ dupilumab vs placebo. EoE-SQ, eosinophilic esophagitis Symptom Questionnaire; LS, least squares; qw, once weekly.

and vomiting) as measured by the EoE-SQ, compared to placebo. At week 24, clinically meaningful reductions were also observed in both emotional and sleep disturbance scores (EoE-IQ). Additionally, more patients on dupilumab reported improvement in their dysphagia symptoms (PGIC) and experienced a reduction in dysphagia severity (PGIS).

Caution

Assessing patient reported outcome measure response for dupilumab, as a newer treatment for EoE, is reasonable. Analogous to other inflammatory conditions of the luminal gastrointestinal tract, there are multiple domains to assess treatment efficacy: endoscopic improvement, reduced inflammation on biopsy, and clinical symptom improvement. The main caution that I have in interpreting this study is that the comparison was performed between people getting placebo vs dupilumab. Realistically speaking, the average gastroenterologist is not going to compare dupilumab efficacy against a lack of EoE treatment; it would need to be compared against dietary modification, swallowed steroid, or PPI. A similarly designed study would involve comparison of dupilumab with these other EoE interventions.

My Practice

This trial offers a new dimension by which to consider any EoE therapy administration, a patient's perception of dysphagia symptoms. As gastroenterologists, we naturally pay attention first to the elimination of eosinophils from mucosal specimens on high powered microscopy. In some respects, this is too narrow a focus. Understanding how the patient's symptoms, impression of dysphagia, and symptom frequency evolves with treatment is key to ensuring long term adherence. It can also be the first marker before endoscopy for a need to consider worsening EoE-related control.

Let's use the most restrictive example of EoE treatment – a dietary elimination diet. Patients desiring EoE management without medications can be faced with the possibility of needing to spend the rest of their lives avoiding at every meal encounter a host of pleasurable foods in order to keep uncontrolled EoE at bay. Perhaps after the first emergency department visit for food impaction (at which time, I would like to remind trainee readers/listeners that a biopsy should almost always be performed to reduce a delay in EoE diagnosis), one may be motivated out of fear to be faithfully adherent to such a a treatment path. Will one want to continue doing that for 1-year out from the impaction? 10-years out? Will clinicians assume permanent adherence on the part of a patient?

This study would encourage me to consider using patient reported outcome measures serially over the time I spend caring for patients with EoE, to track progress and encourage adherence. To date, I must admit that I have generally

focused on whether the last gastroscopy had resolution of eosinophils on biopsy specimens. After reviewing this study, if I notice increased symptom burden or worsened impressions of dysphagia, this may prompt me to consider expedited gastroscopy to repeat tissue sampling and adopt serial patient reported outcome measurement. Alternatively, if someone is becoming increasingly frustrated with having to modify diet, swallow steroids, or take proton pump inhibitors, one can show a favorable trend in measures to help promote treatment adherence.

Unfortunately, given commercial and public insurance formulary vagaries, my practice would not alter based on this study towards earlier adoption of dupilumab as a treatment for EoE (with exceptions possibly for concomitant atopy, eczema, and/or asthma).

For Future Research

While it would be impossible to blind the following study, it would be of interest to compare changes in patient reported scores and disease perception in patients receiving dupilumab compared to other EoE interventions. EoE management options can be so drastically different—diet, steroid, acid suppression, or monoclonal antibody therapy. Some people find dietary modification to be too challenging, are perhaps (too inappropriately) worried about largely theoretical long term acid suppression risk or infection/bone density risk with steroids or would find injections troublesome. If one agent showed the clearest improvement in scores or symptom perception, that may alter the practice of EoE management in the years to come.

Conflict of Interest

The authors have no reported conflicts of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Mirikizumab Is Safe and Effective for Moderate-to-Severe Crohn's Disease

Dr. Rahul Dalal
Associate Editor

Rahul Dalal, MD, MPH

Instructor, Division of Gastroenterology, Hepatology, and Endoscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

IBD

This summary reviews Ferrante M, D'Haens G, Jairath V, et al. Efficacy and safety of mirikizumab in patients with moderately-to-severely active Crohn's disease: A phase 3, multicentre, randomised, double-blind, placebo-controlled and active-controlled, treat-through study. Lancet. 2024;404(10470):2423-2436. .

Correspondence to Rahul Dalal, MD, MPH, Associate Editor. Email: EBGI@gi.org

Keywords: Crohn's disease, mirikizumab, randomized controlled trial

STRUCTURED ABSTRACT

Question: Is mirikizumab safe and effect for moderate-to-severe Crohn's disease?

Design: Phase 3, randomized, placebo and active-controlled treat-through trial.[1]

Setting: The study took place in 324 centers across 33 countries.

Patients: Overall, 1,150 adults of aged 18-80 years with moderate-to-severe Crohn's disease and prior exposure to 1 or more biologic or conventional therapies were included.

Exposure or Interventions: Patients were randomized 6:3:2 to mirikizumab 900

mg induction followed by 300 mg every 4 weeks maintenance, ustekinumab 6 mg/kg induction followed by 90 mg every-8 weeks maintenance, or placebo.

Outcomes: Co-primary endpoints were the composite of patient-reported outcome (PRO) clinical response at week 12 with endoscopic response at week 52 (endoscopic response-composite), and composite of PRO clinical response at week 12 with Crohn's Disease Activity Index (CDAI) clinical remission at week 52 (CDAI clinical remission-composite).

Data Analysis: Adjusted risk differences were calculated and comparisons were performed using the Cochran-Mantel-Haenszel test with non-responder imputation.

Funding: Eli Lilly and Company.

Results: Both co-primary endpoints were met for mirikizumab versus placebo: endoscopic response-composite 38.0% vs 9.0% (P <0.01) and CDAI clinical remission-composite 45.4% versus 19.6% (P <0.01) (Figure 1A). Results were similar regardless of prior exposure to biologics. Mirikizumab demonstrated non-inferiority versus ustekinumab for clinical remission by CDAI at week 52 (Figure 1B). In patients with prior biologic therapy failures, mirikizumab showed numerically higher response rates versus ustekinumab that were not statistically significant. Adverse events for mirikizumab were less common than for placebo and consistent with the known, favorable safety profile of mirikizumab.

COMMENTARY

Why Is This Important?

This study demonstrates both the efficacy and favorable safety profile of another therapy in the IL-23 inhibitor class for Crohn's disease. Importantly, the study demonstrated efficacy regardless of prior bio exposure, indicating that this would be a reasonable option in patients with prior biologic failures. The treat-through design rather than re-randomization after induction mimics clinical practice, and therefore the outcomes observed in the study may be more likely to reflect real-world outcomes. The study also utilized an active control arm, demonstrating non-inferiority to ustekinumab for clinical remission.

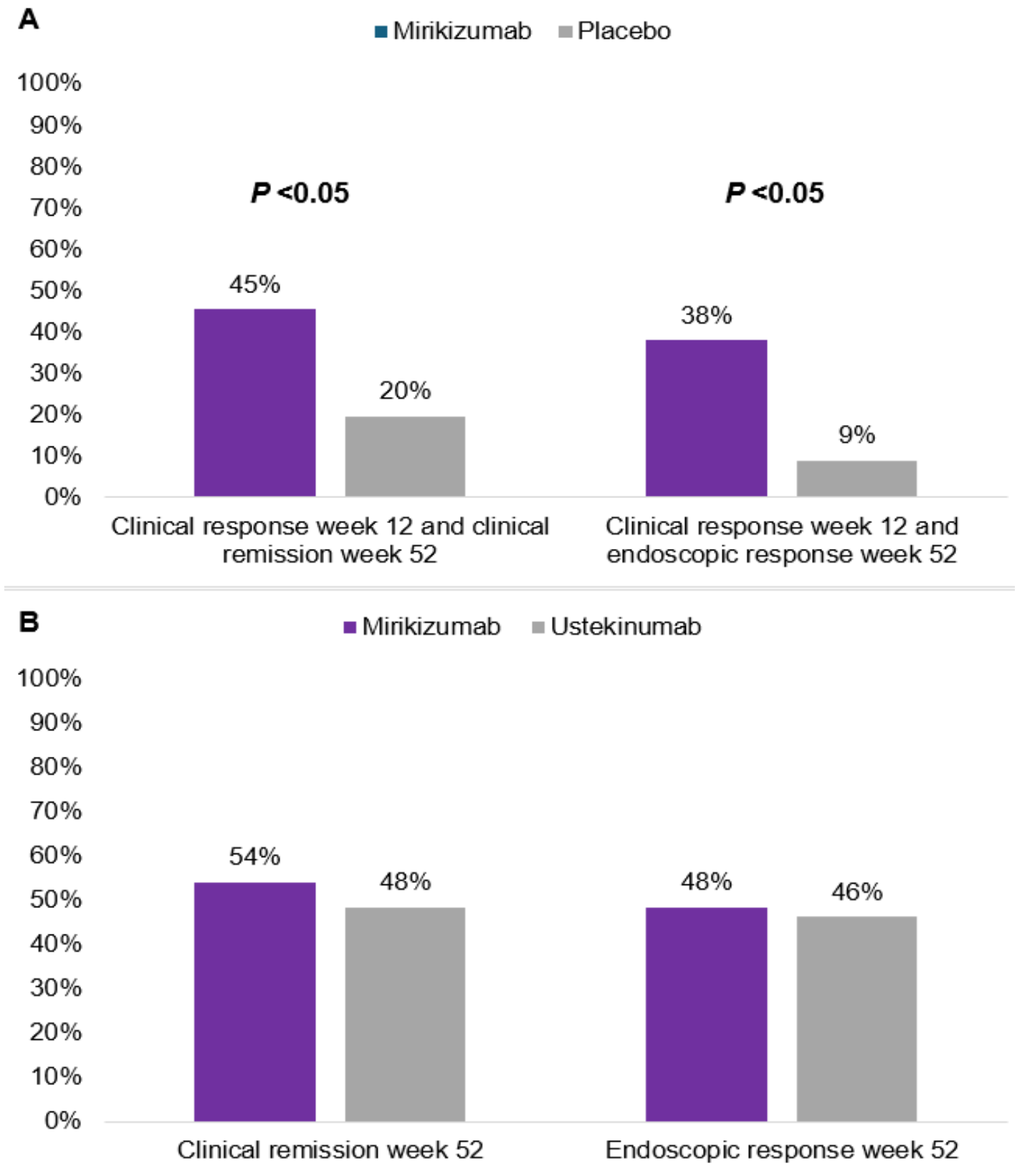

Figure 1. A. Coprimary endpoints for mirikizumab vs placebo. B. Mirikizumab vs Ustekinumab comparisons.

Key Study Findings

The study found that at week 12, a higher proportion of patients receiving mirikizumab achieved a PRO clinical response compared to placebo. At week 52, more patients on mirikizumab reached endoscopic response and CDAI clinical remission compared to placebo. Mirikizumab also demonstrated non-inferiority to ustekinumab in achieving clinical remission and endoscopic response at week 52.

In the bio-exposed population, more patients treated with mirikizumab achieved CDAI clinical remission and endoscopic response compared to those receiving ustekinumab, but this did not reach statistical significance. Patients treated with mirikizumab did achieve significantly more improvements in baseline fecal calprotectin and C-reactive protein compared to those receiving ustekinumab.

The safety of mirikizumab was consistent with its known profile in ulcerative colitis. The most common adverse events included COVID-19, anemia, arthralgia, headache, upper respiratory tract infection, nasopharyngitis, and injection site reactions

Caution

The study used composite endpoints which can be difficult to interpret for real-world practice. Additionally, the study was not powered to detect significant differences between mirikizumab and ustekinumab for bio-exposed patients, which requires further study. Extended intravenous induction or re-induction were not investigated for patients with partial response or loss of response, and this will be investigated in future long-term extension studies.

My Practice

In my practice, I am increasingly utilizing IL-23 inhibitors such as risankizumab as both first and second-line therapies for moderate-to-severe Crohn's disease due to their demonstrated efficacy in both clinical trials and real-world studies.[2-4] It is quite helpful to have another available agent approved in this treatment class. In most instances, I will likely choose mirikizumab over ustekinumab given the numerical improvements in clinical, endoscopic, and biochemical parameters favoring mirikizumab among the bio-exposed, though many of these results did not achieve statistical significance. However, I would need to see head-to-head data before I would consider mirikizumab over risankizumab for Crohn's disease.

For Future Research

Given the expansion of the IL-23 class (including ustekinumab, mirikizumab, risankizumab, and guselkumab), we need additional head-to-head data both within and outside of this treatment class to help guide positioning of advanced therapies. Data is also needed regarding the effectiveness of one IL-23 inhibitor after failure of another (e.g. the effectiveness of mirikizumab after

risankizumab failure and vice versa).

Conflict of Interest

Dr. Dalal has research grant support from Janssen and Pfizer and has served as a consultant for Janssen, Takeda, and Centaur Labs.

Note: The author of this summary is active on social media. Tag him to discuss this EBGI piece.

@RahulSDalalMD

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